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09/214,124	03/17/1999	MARCELO LOPEZ LASTRA	017753-109	5944

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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1632	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Offic Action Summary	Application No.	Applicant(s)	
	09/214,124	LOPEZ LASTRA ET AL.	
	Examiner	Art Unit	
	Quang Nguyen	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-19,25-29,31-35,40-45 and 47-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-19,25-29,31-35,40-45 and 47-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed November 15, 2001 in Paper No. 13 has been entered.

Amended claims 8-19, 25-29, 31-35, 38, 40-45 and 47-51 are pending in the present application, and they are examined on the merits herein.

Following is a new ground of rejection.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-13, 16-19, 25-27, 31-33, 38, 40-43, 47-48 and 51are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to a vector or a viral particle for the expression of one or more genes of interest comprising a nucleotide sequence isolated from the 5' end of the genomic RNA of a reticuloendotheliosis virus (REV) or from the 5' end of the proviral DNA of a reticuloendotheliosis, an isolated cell comprising the same, a method for the preparation of one or more polypeptides of interest by recombination techniques using said isolated cell as well as methods for providing an internal ribosome entry site to a vector and for allowing or activating the encapsidation of a retrovirus using the same nucleotide sequence isolated from the 5' end of the genomic RNA of a reticuloendotheliosis virus (REV) or from the 5' end of the proviral DNA of a reticuloendotheliosis. As defined by the instant invention, REV viruses comprises various type A, B and T subtypes as well as the DIAV, SNV and CSV viruses (see specification, page 7, lines 9-21). Apart from the characterization of an internal ribosomal entry segment within the 5' leader of avian reticuloendotheiosis virus type A, the specification fails to disclose a representative number of species of nucleotide sequences isolated from the 5' leaders of a broad genus of a reticuloendotheliosis virus that possess activities associated with IRES and/or activation of the encapsidation of a retrovirus as contemplated by Applicants, including those derived from naturally occurring reticuloendotheliosis virus variants of various subtypes that have yet been discovered. At the effective filing date of the present application, the art does not provide such teachings in this regard. Possession may be shown by actual reduction to

practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a representative number of species of nucleotide sequences isolated from the 5' leaders of a broad genus of a reticuloendotheliosis virus that possess IRES and retroviral encapsidation activities apart from the 5' leader of an avian reticuloendotheliosis virus type A disclosed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

Claims 8-19, 25-28, 31-35, 38, 40-45 and 47-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(1) A vector or a viral particle for the expression of one or more genes of interest comprising a nucleotide sequence isolated from the 5' end of the genomic RNA of an avian reticuloendotheliosis virus type A (REV-A) or from its DNA equivalent in which U nucleotides in the genomic RNA are replaced by T nucleotides, wherein said nucleotide sequence comprises nucleotides 452-578 of SEQ ID NO:2 and said 5' end extends from the site of initiation of transcription to the initiation codon of the gag gene of said REV-A; an isolated cell comprising the same and a method for the preparation of one or more polypeptides of interest in cultures using the same;

(2) A method for providing an internal ribosome entry site (IRES) to a vector for the transfer and expression of one or more genes of interest, comprising the step of introducing into said vector a nucleotide sequence isolated from the 5' end of the genomic RNA of an avian reticuloendotheliosis virus type A (REV-A) or from its DNA equivalent in which U nucleotides in the genomic RNA are replaced by T nucleotides, wherein said nucleotide sequence comprises nucleotides 452-578 of SEQ ID NO:2 and said 5' end extends from the site of initiation of transcription to the initiation codon of the gag gene of said REV-A;

(3) A method of allowing or activating the encapsidation of a retrovirus or of a retroviral vector, comprising the step of introducing into said retrovirus or retroviral vector, a nucleotide sequence isolated from the 5' end of the genomic RNA of an avian reticuloendotheliosis virus type A (REV-A) or from its DNA equivalent in which U nucleotides in the genomic RNA are replaced by T nucleotides, wherein said nucleotide sequence comprises nucleotides 265 and 578 of SEQ ID NO:2 and said 5' end extends

from the site of initiation of transcription to the initiation codon of the gag gene of said REV-A;

does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 8-19, 38, 40-45 and 47-51 are drawn to a vector or a viral particle for the expression of one or more genes of interest comprising a nucleotide sequence isolated from the 5' end of the genomic RNA of a reticùloendotheliosis virus (REV) or from the DNA equivalent of said genomic RNA, wherein said nucleotide sequence comprises all or part of the region of said 5' end which extends from the site of initiation of transcription up to the initiation of the gag gene, an isolated cell comprising the same, a method for the preparation of one or more polypeptides of interest by recombination techniques using said isolated cell.

Claims 25-28 are directed to a method for providing an internal ribosome entry site (IRES) to a vector for the transfer and expression of one or more genes of interest, comprising the step of introducing into said vector a nucleotide sequence isolated from the 5' end of the genomic RNA of a reticuloendotheliosis virus (REV) or from the DNA equivalent of said genomic RNA, wherein said nucleotide sequence comprises all or part of the region of said 5' end which extends from the site of initiation of transcription up to the initiation codon of the gag gene.

Claims 31-35 are drawn to a method of allowing or activating the encapsidation of a retrovirus or of a retroviral vector, comprising the step of introducing into said retrovirus or retroviral vector, a nucleotide sequence isolated from the 5' end of the genomic RNA of a reticuloendotheliosis virus (REV) or from the DNA equivalent of said genomic RNA, wherein said nucleotide sequence comprises all or part of the region of said 5' end which extends from the site of initiation of transcription up to the initiation codon of the gag gene.

The specification discloses the construction of mono- and dicistronic vector plasmids comprising the 5' non-translational leader of avian reticuloendotheliosis virus type A (REV-A) and characterizes the Internal Ribosomal Entry Segment (IRES) within said 5' non-translational leader. It appears that the minimal IRES sequence resides within a fragment (nucleotides 452-578 of SEQ ID NO:2) of the 5' leader. The specification further discloses the construction of series of retroviral vectors comprising the REV-A sequences containing the minimal IRES site. The retroviral vectors possess either Mo-MLV type LTRs (pREV HW vector series) or spleen necrosis virus (SNV) type LTRs (pMC vector series not disclosed). The infectious viral particles generated from these retroviral vectors were used to determine the viral titer and the expression of reporter genes (placental alkaline phosphatase and neo). The specification teaches that retroviral vectors comprising both a REV-A sequence (nucleotide fragments 265-578 or 452-578) and a conventional encapsidation region (Mo-MLV or VL30) produce viral particles at high titer. Furthermore, it appears that the REV-A sequence ranging from nucleotides 265 to 578 is able to enhance the encapsidation of the viral RNAs and

consequently the higher viral titer in comparison with the control vector pEMCV-CBTV comprising the EMCV IRES site. In comparison with the same control vector, the dicistronic retroviral vector pREV HW-3 comprising REV-A IRES sequence 265-578, is significantly more efficient in transducing reporter genes *in vitro* in the human cell line Dev, derived from a human primary tumor of neuroectodermal origin, whose cells behave like pluripotent stem cells. The specification further discloses that the expression of the reporter genes was unaffected by the differentiation state of these Dev cells.

The above evidence has been noted and considered. However, it can not be reasonably extrapolated to the instant broadly claimed invention for the following reasons.

The instant broad claims encompass the make and use of any nucleotide sequence isolated from the 5' end of the genomic RNA of a reticuloendotheliosis virus (REV) or from the DNA equivalent of said genomic RNA. The instant specification is not enabled for such a broadly claimed invention for the reasons already set forth in the lack of Written Description section above. With the lack of sufficient guidance provided by the present disclosure, it would require undue experimentation for one skilled in the art to make and use the full scope of the instant claimed invention.

The broad claims encompass all or part of the region of the 5' end of the genomic RNA of a reticuloendotheliosis virus, with a preferred embodiment using at least 100 nucleotides and at most 800 nucleotides identical to SEQ ID NO:1, for providing an internal ribosome entry site to a vector or for allowing or activating the encapsidation of

a retrovirus. The instant specification is not enabled for such a broadly claimed invention because apart from disclosing the minimal IRES sequence in the 5' leader of avian REV-A resides between nucleotides 452-578 of SEQ ID NO:2, and an element interacting positively with the encapsidation might be present between nucleotides 265 and 452 of SEQ ID NO:2 (see example 2), the present specification fails to provide sufficient guidance for a skilled artisan on how to make and use any part of the region of the 5' end of the genomic RNA of a reticuloendotheliosis virus, or any nucleotide sequence of at least 100 nucleotides in length or any modifications (including deletion, insertion or substitution) of SEQ ID NO:1 or SEQ ID NO: 2 to obtain the desired IRES and/or retroviral encapsidation activities. As is well recognized in the art, any modification (even a "conservative" substitution) to a critical structural region is likely to significantly alter its functional properties. The present disclosure fails to provide sufficient guidance with regard to which "particular" nucleotide changes (substitution, deletion or insertion) at which position and at which combinations, such that the variant nucleotide sequences could still possess the desired functions, for this instance the IRES and retroviral encapsidation functional properties. Nor is there any evidence of record indicating that apart from the nucleotide sequences containing residues 452 to 578 and residues 265 to 452 of SEQ ID NO: 2, other sequences present in 5' leader of avian REV-A can possess IRES and/or retroviral encapsidation activities. Additionally, there is a high degree of unpredictability associated with the make and use of the claimed embodiment. This situation is similar to the unpredictability in making of a protein or a peptide variant having the desired functional property. In discussing

peptide hormones, Rudinger has stated that "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted a priori but must be determined from case to case by painstaking experimental study (Page 6, first sentence of Conclusions *In* J.A. Parsons, ed. "Peptide hormones", University Park Press, 1976). This unpredictability is further underscored by the fact that the relationship between the sequence of a peptide and its tertiary by the fact that the relationship between the sequence of a peptide and its tertiary structure (or its activity) is not well understood and is not predictable (Ngo et al., *In* K. Merz et al., ed. "The protein folding problem and tertiary structure prediction", Birkhauser, 1994, 491-495). Moreover, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Therefore, with the lack of guidance provided by the instant specification, it would require undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

With respect to claims 12-15 and 48-49, they encompass various components (a) to (f) or (a) to (h) in various combinations within a retroviral vector of the presently claimed invention since as written the claims are not limiting the components to be operatively linked in the recited order. The instant specification is not enabled for such

a broadly claimed invention because it fails to provide sufficient guidance for a skilled artisan on how to make and use the various combinations of the components in a functional manner as encompassed within the full scope of the retroviral vector as claimed. As such, it would require undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

Regarding to claims 16 and 50 encompassing a retroviral vector comprising a retroviral 5' LTR derived from an REV virus and a retroviral 3' LTR of any origin, the specification fails to provide sufficient guidance for a skilled artisan on how to make and use of such a retroviral vector. On the basis of evidence of record, it is unclear what is the beneficial use for such a retroviral vector as claimed. Moreover, due to the replication mechanism of a retroviral virus, viral particles generated from such a retroviral vector would not possess heterologous 5' LTR and 3' LTR due to the duplication of the 3' LTR. Given the lack of guidance provided by the instant disclosure, it would require undue experimentation for a skilled artisan to make and use the full scope of the present broadly claimed invention.

Accordingly, with the lack of guidance provided by the instant specification regarding to the issues set forth above, and the breath of the claims, it would have require undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-19, 25-29, 31-35, 38, 40-45 and 47-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 8, 25, 31 and their dependent claims, the phrase "from the site of initiation of transcription up to the initiation codon of the gag gene" is unclear. Which site of initiation of transcription? And which gag gene? Furthermore, the phrase "the DNA equivalent of said genomic RNA" is also unclear. What exactly does the DNA equivalence encompass or not encompass? The metes and bounds of the claims can not be clearly determined.

In claim 14, it is unclear what is the connection between the limitations (i), (ii) and (iii) with the rest of the claim. Note that the claim recites the IRES site comprises a nucleotide sequence which is identical to the sequence presented in the sequence identifier SEQ ID NO:2.

In claim 15, the phrase "the IRES site comprises a nucleotide sequence identical to the sequence presented in sequence identified SEQ ID NO:2 or to the DNA equivalent of said sequence, starting at nucleotide 265 and ending at nucleotide 578" is unclear. How can the IRES site comprises a nucleotide sequence identical to the sequence presented in sequence identified SEQ ID NO: 2 (nucleotides 1 to 578) and at the same time said nucleotide sequence starts at nucleotide 265 and ending at nucleotide 578? Similarly, in claim 49, for the same reason how can the IRES site comprises a nucleotide sequence identical to the sequence presented in sequence identified SEQ ID NO: 2 (nucleotides 1 to 578) and at the same time said nucleotide

sequence starts at nucleotide 452 and ending at nucleotide 578? Clarification is requested.

Claims 18 and 19 recite the limitation "a viral vector according to claim 8" in lines 1 and 2 of the claims. There is insufficient antecedent basis for this limitation in the claim. Claim 8 is directed to a vector not a viral vector.

In claim 29, it is unclear what is the connection between the limitation (i), (ii) and (iii) with the rest of the claim. Note that the claim recites said nucleotide sequence is identical to the sequence presented in the sequence identifier SEQ ID NO:2 (nucleotides 1 to 578). Similarly, it is also unclear in claims 35 and 45 what is the connection between the limitation (i), (ii) and (iii) with the rest of the claim for the same reasons. Clarification is requested.

In claim 40, it is unclear what is encompassed by the phrase "a pharmaceutical composition prepared from said vector or viral particle". What are the components present or not present in the pharmaceutical composition? The metes and bounds of the claim can not be clearly determined. Additionally, the claim recites "a viral particle generated from a viral vector according to claim 8" which lacks antecedent basis for this limitation because claim 8 is not directed to a viral vector.

In claim 50, the phrase "a nucleotide sequence which is identical to the sequence presented in sequence identifier SEQ ID NO:2 or to the DNA equivalent of said sequence, starting at nucleotide 265 and ending at nucleotide 578 as encapsidation region" is unclear. How can a nucleotide sequence identical to the sequence presented in sequence identifier SEQ ID NO: 2 (nucleotides 1 to 578) and at the same time said

nucleotide sequence starts at nucleotide 265 and ending at nucleotide 578? The metes and bounds of the claim can not be clearly determined.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on November 15, 2001 in Paper No. 13 (pages 11-13) have been fully considered. However, Examiner respectfully finds Applicants' arguments to be unpersuasive for the following reasons.

With respect to the issue of the 5' end of the genomic RNA of a reticuloendotheliosis virus, Applicants argued that a skilled person would have known that the site of initiation of transcription represents the first nucleotide which follows the U3 domain of the 5'LTR, and that more specifically concerning REV retrovirus, the referred sequence extending from the transcription initiation site up to the initiator codon of the gag gene. However, as written, the claims still do not clearly define the 5' end of the genomic RNA of a reticuloendothliosis virus as explained by Applicants.

With respect to the phrase "DNA equivalent of said genomic RNA", Applicants argued that this phrase refers to the translation of an RNA sequence into a DNA sequence by replacing U nucleotides by T nucleotides in the sequence of the concerned genomic RNA. As written, the claims do not recite as such and since the phrase "DNA equivalent" is not clearly defined in the instant specification, it is uncertain what the DNA equivalence encompass or not encompass? The metes and bounds of the claims can not be clearly determined.

Claim Rejections - 35 USC § 102

Claims 8, 9, 18 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Dornburg (WO 94/29437).

The claims are drawn to a vector or a viral particle for the expression of one or more genes of interest comprising a nucleotide sequence isolated from the 5' end of the genomic RNA of a reticuloendotheliosis virus (REV) or from the DNA equivalent of said genomic RNA, wherein said nucleotide sequence comprises all or part of the region of said 5' end which extends from the site of initiation of transcription up to the initiation of the gag gene, and an isolated cell comprising the same.

As written, the claims read on the teachings of Dornburg who discloses the preparation of highly-efficient, self-inactivating, recombination-free, U3-free retroviral vectors or viral particles derived from spleen necrosis virus (a reticuloendotheliosis virus) comprising part of the region of the 5' leader of the spleen necrosis virus which extends from a first nucleotide at the boundary between U3 and R to the initial codon of the gag gene (see pages 4, 9 and Figure 3). Dornburg also teaches harvesting the viral particles from helper cells transfected with the viral vectors (page 10).

The aforementioned teachings meet the limitation recited in the instant broad claims, and therefore Dornburg anticipate the instant claimed invention.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER